



The University of Oklahoma
Health Sciences Center

ENDOCRINOLOGY, METABOLISM AND HYPERTENSION SECTION
DIVISION 55 MAR 19 11:54

March 1, 1999

RE: Docket Number 98P-0622

Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Resources
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

To Whom It May Concern:

As a clinician who has been intensively involved in the care of patients with diabetes for almost 20 years, I am compelled to rebut the petition submitted by Sidney Wolfe and his organization "Public citizen Health Research Group" to withdraw Troglitazone ("Rezulin") from the market. Over the course of my 20 years of practice, it has been obvious to me that Type 2 diabetes was a progressive disease requiring escalation of therapy every year or so in an attempt to get once controlled diabetes back under control. I have come to appreciate that this was due to the fact that none of the agents we had available for the therapy of Type 2 diabetes prior to 1997 addressed the underlying pathophysiology, insulin resistance years prior to the availability of Rezulin. As a diabetologist, the in vitro and animal data suggesting that troglitazone would improve the metabolic responses to insulin made me anxious to add this drug to the limited armamentarium available to me to try to control hyperglycemia in these difficult patients. Since the introduction of troglitazone in 1997, I have not been disappointed in the influence this agent has had on my ability to get previously uncontrollable patients controlled. As more data has been available on attenuation of the associated co-morbidities of increased blood pressure, elevated triglycerides and low HDL cholesterol, I have come to appreciate that this agent is the first specific therapy we have had for Type 2 diabetes. It is now obvious to me that the thiazolidinediones should be the cornerstone of our therapy of Type 2 diabetes with other agents used as adjuvants in those patients who can not be managed with monotherapy as they function at other sites of the pathophysiology, primarily at the acquired relative insulin deficiency. Excitingly the most recent data of improved β cell function after therapy with troglitazone, a shift in the pattern of LDL particles from the most atherogenic, small dense LDL (Pattern B) to the larger, lighter (Pattern A), reductions in fibrinogen and PIA-1 as well as reduction in the intimal-medial thickness of carotid arteries, portend even greater cardiovascular benefit with this agent than would be predicted by comparable metabolic control achieved by other agents.

Dr. Wolfe's position fails to put into perspective the mortality of untreated Type 2 diabetes in 2,000 deaths/100,000 patients years or that even with therapy, 150,000 of the 16 million patients with diabetes die from this disease and its associated complications each year. This is a life-threatening disease and a certain level of toxicity has to be acceptable we would have few approved therapies for this deadly disease. While the liver in

98P-0622

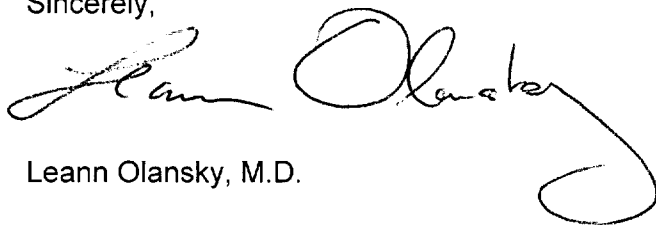
CS

jury of troglitazone can be life-threatening, it fortunately has been rare (one in forty thousand patients) if none on the currently recommended monitoring is undertaken, I find that Parke-Davis has taken a very responsible and ethical position in warning practitioners to monitor ALT levels monthly for the first 8 months, then every 2 months for the rest of the first year. It is my understanding that this has brought the hepatic-related deaths to under one per 100,000 patients. Not only have their representatives repeatedly reminded me and other practitioners to do this but the company has given unequivocal guidelines about levels of ALT above which the agent should not be started, as well as what action to take if ALT rises about 1.5 x ULN and recommending discontinuation if ALT exceeds 3 x the ULN and advises physicians not rechallenge patients who have reached these levels. This is much more than the "Dear Doctor" letter sent when the issue of liver injury from NSAIDs was again addressed after Duract had entered the market and demonstrated this toxicity shared with other agents of this class. It is true that Duract was withdrawn but the other members of this class remaining share the potential for severe liver injury, even death or the need for liver transplant yet this important class of agents capable of relieving considerable human suffering has not been withdrawn; some members are even over the counter medications. Undoubtedly, not every elevation of ALT more than 3X the upper limit of normal seen in patients on troglitazone is hepatic toxicity capable of causing liver failure, but the recommendations are conservative and made to minimize the risk to patients.

I am of the opinion that Dr. Wolfe is in error in his estimate that only 10% of severe adverse reactions are reported to the FDA. This may be true of older drugs, especially when the specific adverse has been fairly well established. With new agents, the opposite is likely true. Toxicity is often attributed to the newest agent added by the potential for over-reporting. This patient population is rarely on a single agent. Fatty liver is a common concomitant condition. The media spotlight on this agent generated in part by Dr. Wolfe and his organization assures that any hepatic failure a patient on Troglitazone will be reported.

I do not wish to minimize the seriousness of even one iatrogenic patient death, but it is most important that the committee put the rather rare occurrence (reduce further reduced by the pharmaceutical company guidelines for liver monitoring) in the perspective of the very serious life-threatening disease treated by this agent. There are patients likely dying daily due to lack of aggressive therapy of this disease. I plead with the committee not to withdraw this important weapon we have recently acquired in our fight against this terrible disease.

Sincerely,

A handwritten signature in black ink, appearing to read "Leann Olansky". The signature is fluid and cursive, with a large loop at the end of the last name.

Leann Olansky, M.D.



The University of Oklahoma
Health Sciences Center

Department of Medicine
Endocrinology, Metabolism and Hypertension Section
Post Office Box 26901
Oklahoma City, Oklahoma 73190-3048



Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Resources
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

20857/0003

